Section of General Practice

President D L Crombie MD

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Albert Wander Lecture

Abstract: Dr Hope-Simpson presents a study of all cases of herpes zoster occurring in his general practice during a sixteen-year period. The rate was 3·4 per thousand per annum, rising with age, and the distribution of lesions reflected that of the varicella rash.

It was found that severity increased with age, but that the condition did not occur in epidemics, and that there was no characteristic seasonal variation. A low prevalence of varicella was usually associated with a high incidence of zoster.

Dr Hope-Simpson suggests that herpes zoster is a spontaneous manifestation of varicella infection. Following the primary infection (chickenpox), virus becomes latent in the sensory ganglia, where it can be reactivated from time to time (herpes zoster). Herpes zoster then represents an adaptation enabling varicella virus to survive for long periods, even without a continuous supply of persons susceptible to chickenpox.

The Nature of Herpes Zoster: A Long-term Study and a New Hypothesis

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Concerning Dr Albert Wander

The present lecture inaugurates a series instituted through the generosity of the Dr Albert Wander Charitable Fund in memory of the founder of the firm of Wander. You will wish me to preface the lecture with a word about this remarkable man. Mr Robert Thomson kindly obtained the information from another Dr Albert Wander, grandson of the founder of the firm.

Our Albert Wander was born in Switzerland in 1867. He founded the pharmaceutical house that bears his name in Berne, and daughter companies were subsequently established in other countries, including Britain. A man of wide cultivation, actively devoted to the sciences, keenly interested also in the arts and literature, he was a Doctor of Philosophy and was awarded an honorary doctorate in Medicine by the University of Berne and another in Philosophy by the University of Zurich. Feeling a need to contribute still further to his wide field of interest he created, first through the mother house in Berne, and later through daughter companies, funds with the following objectives: the relief of poverty; the advancement of education; the advancement of religion; other purposes beneficial to the community.

In April 1925 he instituted the fund of his London Company, the patron of the lecture which the Trustees have done me the honour of inviting me to deliver. I am deeply grateful for the opportunity of honouring the memory of Dr Albert Wander in this way, and of paying this brief tribute to his ideals which I cordially share.

Introduction

Herpes zoster is fascinating because it arrives unpredictably, is readily diagnosed – a rare pleasure for most of us – and difficult to explain. This lecture presents a study of all the cases of zoster occurring in our general practice during a sixteen-year period, undertaken in the hope that the natural history of the disease as it appears in an unselected population might cast light upon its nature. Indeed, some of the observations do appear to indicate certain suppositions about the mechanisms underlying the disease, and I have incorporated them into a coherent hypothesis in an attempt to explain zoster. In order to put this into its appropriate setting one must briefly recapitulate such portions of the history of the malady and the previous hypotheses of causation as are relevant.

History

Two major characteristics dominate our knowledge of zoster, namely, the association with the sensory ganglia and the relationship with varicella. Both of these were discovered in the nineteenth century. Richard Bright as long ago as 1831 recognized the implications of the segmental distribution of the rash, and in 1862 von Bärensprung proved the correctness of Bright's deduction by demonstrating at autopsy the damage in the sensory nerve and ganglion. Finally Head & Campbell almost completed this chapter of knowledge when in 1900 they published a magnificent study including detailed post-mortem examinations of 20 persons who had had zoster. All the gross and minute pathology of the disease is described and illustrated: the acute hæmorrhagic inflammation in recently infected ganglia and sensory nerves, the nerve damage linking the affected neurones peripherally to the sensory endings and centrally to the cord and brain, the recovery and the permanent damage. From their experience they were able to map the sensory area related to each ganglion as shown in Fig 1.

The second major characteristic, the association with varicella, was noticed by von Bókay in 1888 (Bókay 1909) and was rapidly confirmed by other observers. The first half of the present century saw the relationship with varicella solidly established although, perhaps because it remained unexplained, many refused to believe that the disease caught from persons with zoster was in fact ordinary varicella. Their reluctance is a little difficult to understand. First Kundratitz in 1925 and then Bruusgaard in 1932 had shown that children inoculated with zoster vesicle fluid might not only themselves develop varicella but also transmit it to their uninoculated companions. In those subjects with a history of varicella, attempts at inoculation had been unsuccessful. In 1944 Abrahamson had stored plasma from a patient convalescent from zoster, and had later used it successfully to protect children in contact with varicella, although the other children in the same ward developed varicella. Taylor-Robinson & Downie (1959) had shown by immunological methods that zoster and varicella are closely related, and histologists had demonstrated the similarity of the skin lesions and the presence of large eosinophilic inclusions in the nuclei of many of the affected cells in both diseases. Yet Seiler (1949), in an epidemiological study in Edinburgh, had concluded that there are two different sorts of varicella, but in 1953, using a different epidemiological approach in the Shetland Islands off Scotland, we found evidence of the identity of the two diseases (Hope-Simpson 1954).

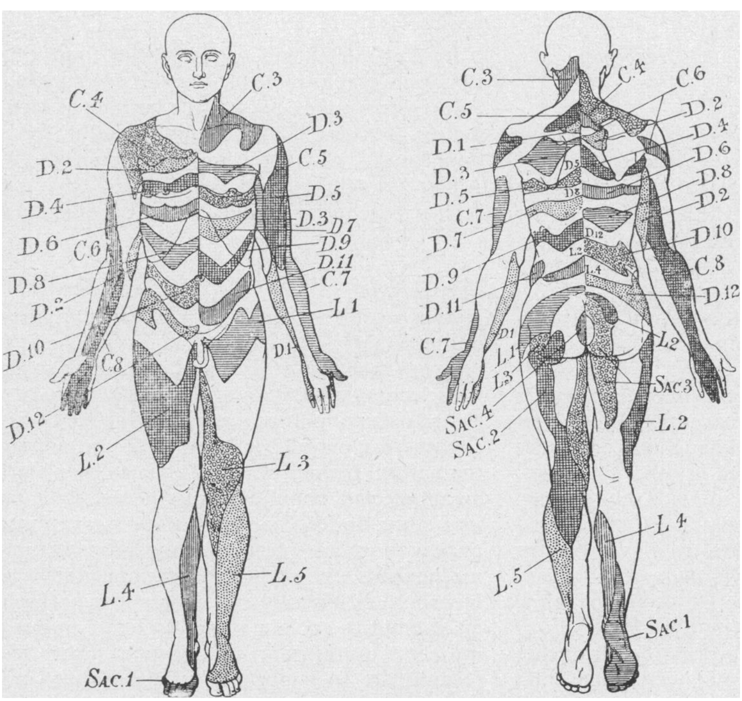

Fig 1 ***Zoster areas allocated to sensory ganglia by Head & Campbell. (Reproduced from Head & Campbell, 1900, by kind permission)***

Table 1
Herpes zoster by months and years – practice figures

Month	*1947*	*1948*	*1949*	*1950*	*1951*	*1952*	*1953*	*1954*	*1955*	*1956*	*1957*	*1958*	*1959*	*1960*	*1961*	*1962*	*Total*
January	1	1	1	3	–	–	1	1	3	–	2	2	–	1	–	–	16
February	–	1	1	–	1	–	1	1	1	–	–	2	1	1	1	1	12
March	1	–	1	–	1	–	–	–	1	1	–	1	1	1	1	1	10
April	–	1	3	2	1	–	2	–	1	2	1	1	1	1	2	1	19
May	1	3	1	1	1	1	2	–	–	–	–	3	1	1	–	–	15
June	2	1	–	2	2	1	–	–	1	–	–	–	1	1	4	1	16
July	–	3	–	1	1	1	–	4	3	–	1	2	–	1	3	4	24
August	–	2	3	1	1	2	3	1	1	3	1	1	1	–	1	1	22
September	6	–	6	1	1	–	–	–	1	–	–	–	1	2	–	1	19
October	2	–	1	–	1	2	1	–	2	–	3	1	–	2	2	1	18
November	2	–	–	1	–	1	–	1	–	2	–	–	1	–	3	–	11
December	1	–	–	–	1	–	1	1	2	2	1	–	–	–	1	–	10
Total	16	12	17	12	11	8	11	9	16	10	9	13	8	11	18	11	192

The controversy was finally settled when Weller & Stoddard (1952) at last succeeded in growing the varicella virus in a tissue culture system, and Weller & Coons (1954) showed that the virus was the same whether it came from a case of varicella or a case of zoster. This is the point at which we stand today.

Various Hypotheses

If varicella is an acute specific infectious disease like measles and mumps, but due to the varicella virus, what is zoster if it also is due to the same virus? Many, impressed perhaps by the fever, the rash, the enlarged glands and the potentiality for transmitting the virus, have regarded it as an alternative acute infection. This hypothesis of zoster as a disease which can be caught has taken two forms, either that zoster may be caught from contact with another case of zoster, or that it may be caught from contact with a case of varicella. A third hypothesis recently increasing in popularity suggests that zoster is not caught at all, but is due to reactivation of latent virus which has remained dormant in the body since the original attack of varicella. The evidence from our field study indicates which of these three possibilities is correct.

The General Picture

With such a striking disease it is likely that I and my partner saw all the cases in our practice of some 3,500 persons in Cirencester, England, and we have not encountered evidence of a missed case. One hundred and ninety-two cases were recorded during the sixteen years 1947–62, which gives an average annual rate of 3·4 per thousand persons. The practice is representative in its composition of the community of this area, and has no special bias as to age, sex or occupation. McGregor (1957) in a general practice study in and around Hawick, Scotland, recorded a higher rate, namely 4·8 per thousand per annum during the seven years from July 5, 1948, to July 4, 1955. It was possible that these years might have had an especially high incidence of zoster, but our own figures recalculated for that period gave the same annual average result as before, 3·4 per thousand. It appears that, in the perhaps more thinly populated regions of Dr McGregor's practice, zoster was nearly half as common again as in Cirencester.

The Influence of Season

Table 1 shows the prevalence of zoster by months and years. There is no perceptible seasonal effect. Zoster occurred in all the months, the lowest figures being for March and December and the highest for July. The differences are not significant and in McGregor's study the picture is similar, except that the maximum and minimum fall in other months. Zoster would therefore appear to have been independent of any seasonal influence.

Examination of the Hypothesis that Zoster Transmits Zoster

Table 1 permits the examination of the hypothesis that zoster is caught from other cases of zoster. Were this the method by which zoster normally appears, it would be bound to come in epidemics, and indeed it is often said to do so. Head & Campbell (1900), amongst others, maintain that there are epidemics of zoster, and argue that it is an acute specific fever *sui generis*. When a small aggregation of cases appears, the disease is so striking that it is apt to give the impression of an epidemic, but examination of Table 1 shows that in our cases this impression was erroneous. Over the whole period of sixteen years, zoster flowed fairly steadily averaging 12 cases annually, with a minimum of 8 cases in 1952 and 1959 and a maximum of 18 cases in 1961. Such aggregations as occur are statistically insignificant.

Another method of examining this hypothesis is to see what happens to persons in close contact with zoster patients. Should direct transmission be occurring, persons in the household of zoster patients would be particularly at risk. Among 318 such domiciliary contacts, no case of zoster was reported to us. Some cases would surely have occurred had they been particularly at risk.

McGregor's study also supports the absence of zoster epidemics. Figures drawn from hospital experience may be misleading, because of the uncertain manner of selection of the patients and insufficient knowledge of the community from which they are drawn.

Examination of the Hypothesis that Varicella Transmits Zoster Directly

If zoster were caught directly not from another case of zoster but from contact with a person with varicella, it should be abundant at times when varicella is epidemic. This certainly was not so in our series, as may be seen from Table 2, which compares the annual prevalences of the two diseases. There were epidemics with more than 100 reported cases of varicella in four of the years. Three of these – 1952, 1957 and 1959 – provided the lowest prevalence of zoster, whereas the fourth, 1961, gave the highest prevalence. Far from coinciding, were it not for 1961 the inverse relationship would be impressive, namely, that years high in varicella tended to be low in zoster and vice versa. At all events, the simple picture of persons with varicella infecting those around them with virus, and so giving them attacks of zoster, may be confidently dismissed, and there may even be a hint of an opposite possibility, namely, that contact with varicella may confer some protection against zoster.

Once again we were able to test the hypothesis more directly. Were persons with varicella transmitting zoster, those around them in the home would be particularly at risk. This would still be true if, as suggested by Barnett (1950) and others, zoster only occurred in those with a waning immunity to varicella. This method of domiciliary contact has been used to determine the infectiousness of the varicella virus, by noting the proportion of susceptibles in the home who catch the disease. In the case of varicella itself, it is about 60%. If varicella patients were also transmitting zoster, even at a much lower rate, a study of all domiciliary contacts would be bound to reveal how actively this was happening. We have records of 1,287 persons in household contact with varicella. Had they been particularly exposed to the risk of picking up a zoster infection, some would certainly have developed zoster, and indeed one or two might even have developed it by chance. As none of them did so, they cannot be considered to have been especially at risk.

Table 2
Annual totals of herpes zoster in the practice and varicella notifications for the Area

Year	*Herpes zoster*	*Varicella*
1947	16	7
1948	12	28
1949	17	30
1950	12	81
1951	11	22
1952	*8*	*193*
1953	11	24
1954	9	89
1955	16	23
1956	10	73
1957	*9*	*191*
1958	13	61
1959	*8*	*101*
1960	11	25
1961	*18*	*106*
1962	11	24

A Warning

Although neither of these two hypotheses can explain the common run of cases of zoster, it is necessary to exercise caution in dismissing them altogether. Rare events are difficult to exclude with certainty, and there may yet be exceptional situations where transmission of virus from a patient with varicella or zoster does cause zoster in another person. In the literature they are too numerous and too circumstantial to be altogether dismissed. I had the opportunity of investigating one such case, which occurred in the practice of Dr R A J Williams of Frome. It concerned a household of three persons, husband and wife, and a maid. The wife, aged 57, developed zoster on July 21, 1947. Eighteen days later the husband, aged 52, developed zoster, and the next day the maid developed chickenpox. Such events, though they occur very seldom, may be of theoretical importance. Nevertheless, one has no right to found a general hypothesis of zoster causation upon rare events, and for practical purposes zoster-varicella transmission is a one-way traffic. Contact with zoster in appropriate persons may cause varicella, but not vice versa. This is the phenomenon which later I hope to explain.

Examination of the Hypothesis of Latency

Having disposed of the other two hypotheses, one is left with the hypothesis of virus latency, probably the most widely accepted explanation at present. The postulation of latency, however, raises some difficult problems. The zoster patient must presumably have suffered an attack of varicella, overt or covert, in order to establish the latent residue of virus which causes his attack of zoster. How then can one explain zoster in childhood?

In the present series 6 patients under 10 years old had zoster. Each had already had an attack of varicella, even a 2-year-old boy who had had chickenpox at 6 months of age. Winkelmann & Perry (1959) record 7 cases of zoster in children aged from 7 months to 5 years, 3 of them only 2 years old. All were found to have a clear history of an earlier attack of varicella, except the 7-month-old baby. Zoster in childhood, therefore, is by no means incompatible with the hypothesis of reactivation from latency, but the 7-month-old baby suggests a more awkward phenomenon, namely, zoster in the newborn.

As long ago as 1889 Lomer reported zoster in a child only 4 days old. The eighth-day ritual circumcision had to be postponed for several weeks because the rash affected the penis. In 1952 Feldman was able to collect 9 neonatal cases from the literature and added a further case of his own. How can latent varicella virus be present so soon after birth? A clue may be found thrown out almost accidentally in some of the accounts. For example, during the third month of her pregnancy the mother of Lomer's infant had been closeted all one day with a friend with severe zoster. The encounter is only mentioned by Lomer as a possible example of psychological prenatal influence, similar to the folk tales of mothers frightened in pregnancy by hares and subsequently producing infants with hare-lip. In Feldman's case the mother recalled that she herself had had an attack of zoster in early pregnancy, or perhaps just before conception. Poulsen (1951) records zoster ophthalmicus in an infant of 15 months who had not had varicella, but his three siblings had had varicella three months before he was born.

It would therefore appear that children with zoster who are 2 years old or more usually give a history of a previous attack of varicella, whereas in younger infants there is often a prenatal history of maternal contact with varicella virus, although the records in such cases tend to be defective.

It is not enough to postulate latency of a dormant virus. The hypothesis needs to be much more detailed to be susceptible of further investigation, and there are many questions to which it should give an answer. Does every attack of varicella leave a legacy of latent virus? If it does so, where does the virus reside, in skin or in sensory ganglion? If resident in the skin, what causes the virus to reactivate? Does it receive impulses from an acutely inflamed ganglion, and if so what has caused the damage in the ganglion? If, on the other hand, virus has been latent all the time in the ganglion itself, how did it get there, and in how many of the ganglia does it reside? How does it reactivate, and why, and when it has reverted, how does it again reach the skin? The hypothesis proposed in this lecture will cover these and other points with successive suppositions detailed enough to be attacked or supported by experiment and epidemiological observation.

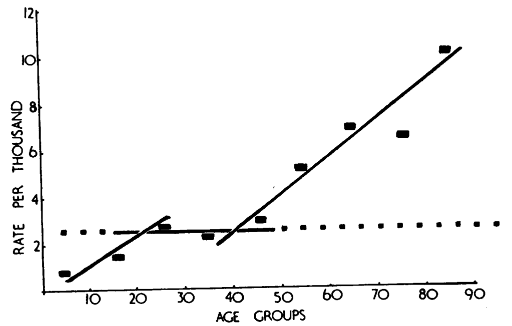

Fig 2 *Age specific incidence of zoster*

The Influence of Age

Fig 2 and Table 3 show that children under 10 years of age were attacked lightly, whereas the 99 octogenarians suffered a rate more than fourteen times higher, 10·1 per 1,000. In between the two extremes, the numbers are insufficient to be certain of the shape of the curve. The steep rise in incidence in the first two decennia may simply represent the progressive proportion of the population which has had an attack of varicella. On the latency hypothesis, a person is not a candidate for zoster until he has had an attack of varicella and so become infected with the virus. At birth almost nobody will be carrying the varicella virus, but before 20 years old almost everyone has become infected. In the first decade most children will be in the state in which they cannot be considered available for zoster, because they have no latent virus, and, therefore, the overall incidence will be low, although amongst those of them who have already had varicella the rate may not differ much from that in the mature age groups. Similarly in the next decade, from 10–19

Table 3
Zoster 1947–62 by age

Age Groups (years)	*Population*	*No. of cases*	*Rate per 1,000*	*Rate per 1,000 per annum*
0–9	510	6	11·8	0·74
10–19	455	10	22·0	1·38
20–29	412	17	41·3	2·58
30–39	491	18	36·6	2·29
40–49	492	23	46·7	2·92
50–59	454	37	81·5	5·09
60–69	350	38	108·6	6·79
70–79	263	27	102·7	6·42
80–89	99	16	161·6	10·10
90–99	8	–	–	–
Total	3,534	192	54·3	3·39

years old, the proportion of persons who have had varicella will have much increased, and the overall incidence, which lies between that in the group under 10 years old and that in the third decade, may simply reflect the increasing proportion of those persons who have had varicella. In the third decade in which almost the whole group has experienced an attack of varicella, almost all are primed with latent virus and are candidates for zoster. The rate in this group of 2·6 per thousand may thus represent the usual incidence of zoster in a fully primed population, and the figures for the next two decades support this suggestion, being 2·3 and 2·9 respectively. A rate of about 2·5 per thousand may therefore be true from childhood to 50 years of age amongst persons who have had varicella. But what a change sets in now! Amongst the 50-year-olds the rate nearly doubles at 5·1, and nearly doubles again in extreme old age. This is a characteristic that may well hold an important clue to the nature of zoster.

The Influence of Sex

Sex is commonly reputed to exert an effect on the incidence of zoster, males being said to suffer more often than females. The present series does not support this view. The average annual rate amongst males was 3·6 per thousand, that amongst females 3·2, and the male preponderance occurred in only five of the decennial groupings. The series of McGregor (1957) and of Burgoon *et al.* (1957) support this conclusion.

The Influence of Anatomical Location

The anatomical location of zoster is of a type to make imperative demands on any explanation of the nature of the disease. Zoster usually attacks the area supplied by a single sensory ganglion, and in order to obtain an accurate attribution of the affected segment, we depicted the rash from life on to standard diagrams of the human body in three positions – front, affected side and back – and then compared our drawings with the chart in Head & Campbell's paper (1900) (Fig 1) and with Cunningham's Textbook of Anatomy. The procedure is subject to numerous inaccuracies. The adult male and female differ anatomically from the sexless diagram, and each sex provides a variety of different physical types. Again, when zoster occurs in small children, the affected segmental area has to be translated on to the adult picture, where physical proportions are very different. As the infant grows and matures, the anatomical regions assume new relationships. Furthermore, the individual neural segments are themselves variable, and there is about 20% overlap between areas served by adjacent ganglia. Despite these difficulties, it is usually possible to allocate the zoster rash to a specific ganglion; the simultaneous involvement of several ganglia is uncommon. When adjacent ganglia appear to be involved, especially around the limbs and face, one should hesitate to make a double attribution because of the variable innervation and, as Weddell & Miller have recently shown (1962), in these situations anastomotic twigs linking adjacent areas are abundant. Indeed, it is a noteworthy characteristic of zoster that an attack upon the single sensory ganglion is common and a multiple attack very rare. It is also noteworthy that when multiple attacks do occasionally occur, the affected segments are usually widely separated and often on opposite sides of the body.

The Incidence on Specific Ganglia

Table 4 and Fig 3 show the distribution of the attacks of zoster on the individual sensory ganglia.

The specific incidence on each pair of sensory ganglia is calculated by ns/N, where N is the

Table 4
Anatomical location

Segment	*Right*	*Left*	*Total*	*Specific incidence*
Cranial				
V.1	11	5	16	2·8
V.2	1	4	5	0·9
V.3	1	3	4	0·7
VII	1	1	2	0·35
Cervical				
1	–	–	–	–
2	1	4	5	0·9
3	3	4	7	1·2
4	2	2	4	0·7
5	2	1	3	0·5
6	2	0	2	0·35
7	1	3	4	0·7
8	1	0	1	0·2
Dorsal				
1	1	1	2	0·35
2	2	1	3	0·5
3	4	4	8	1·4
4	4	1	5	0·9
5	8	8	16	2·8
6	5	7	12	2·1
7	4	5	9	1·6
8	2	8	10	1·8
9	8	4	12	2·1
10	5	6	11	1·9
11	1	0	1	0·2
12	3	4	7	1·2
Lumbar				
1	4	4	8	1·4
2	5	4	9	1·6
3	2	2	4	0·7
4	–	–	–	–
5	1	2	3	0·5
Sacral				
1	1	1	2	0·35
2	1	1	2	0·35
3	0	2	2	0·35
4	–	–	–	–
5	–	–	–	–

Right side, area not stated – 4, 3 of which are in the thorax
Left side, area not stated – 2, both thorax
Area stated, side not stated – 3, V.3, S.5, C.5
Area not stated, side not stated – 4

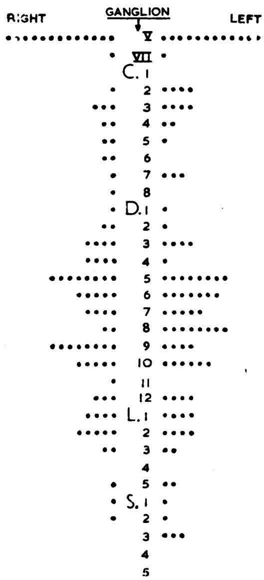

Fig 3 *Segmental location of cases of zoster*

Table 5
Incidence of herpes zoster per ganglion pair

	Cirencester cases			Head & Campbell (1900)			Combined		
Segment	No. of cases	× 30	÷ 154	No. of cases	× 30	÷ 394	No. of cases	× 30	÷ 548
C.1	–	–	–	–	–	–	–	–	–
2	5	150	0·97	1	30	0·08	6	180	0·33
3	7	210	1·36	15	450	1·1	22	660	1·20
4	4	120	0·78	21	630	1·6	25	750	1·37
5	4	120	0·78	2	60	0·15	6	180	0·33
6	2	60	0·39	3	90	0·23	5	150	0·27
7	4	120	0·78	5	150	0·4	9	270	0·49
8	1	30	0·19	–	–	–	1	30	0·05
D.1	2	60	0·39	5	150	0·4	7	210	0·39
2	3	90	0·58	9	270	0·7	12	360	0·66
3	8	240	1·56	34	1020	2·6	42	1260	2·30
4	5	150	0·97	38	1140	2·8	43	1290	2·35
5	16	480	3·12	38	1140	2·8	54	1620	2·96
6	12	360	2·34	20	600	1·5	32	960	1·75
7	9	270	1·75	19	570	1·4	28	840	1·53
8	10	300	1·98	36	1080	2·7	46	1380	2·52
9	12	360	2·34	19	570	1·4	31	930	1·70
10	11	330	2·16	26	780	2·0	37	1110	2·03
11	1	30	0·19	22	660	1·7	23	690	1·26
12	7	210	1·36	18	540	1·4	25	750	1·37
L.1	8	240	1·56	27	810	2·0	35	1050	1·92
2	9	360	2·34	22	660	1·7	31	1020	1·89
3	4	120	0·78	5	150	0·4	9	270	0·49
4	–	–	–	1	30	0·08	1	30	0·05
5	3	90	0·59	2	60	0·15	5	150	0·27
S.1	2	60	0·39	–	–	–	2	60	0·11
2	2	60	0·39	1	30	0·08	3	90	0·16
3	2	60	0·39	5	150	0·4	7	210	0·39
4	–	–	–	–	–	–	–	–	–
5	1	30	0·19	–	–	–	1	30	0·05

number of cases in the whole series, *n* the number of attacks affecting a particular ganglion pair, and *s* the total number of pairs of ganglia under consideration.

Laterality has no influence, for in 91 cases the right side was attacked and in 94 the left side (in 7 the side was not recorded). Two important phenomena are apparent in Fig 3: (1) The individual ganglia are not attacked at random; some areas suffer far more frequently than others. (2) Despite all the difficulties and uncertainties attending the collection of the data, the figure is remarkably symmetrical, so that the left side supports the conclusions of the right, and one is forced to the opinion that the differences in incidence between one anatomical area and another are real and not random. The V cranial nerve and the trunk from D.3 to L.2 are more heavily attacked than the segments supplying the limbs. Head & Campbell (1900) give segmental allocations for 394 cases, omitting those that attacked the cranial segments. The agreement between their series and ours is excellent, and Table 5 and Fig 4 show the two series combined. The incidence changes abruptly from one region to another. For example, between D.2 and D.3 where the upper limb joins the trunk, the rate jumps threefold from 0·66 to 2·30. Similarly at

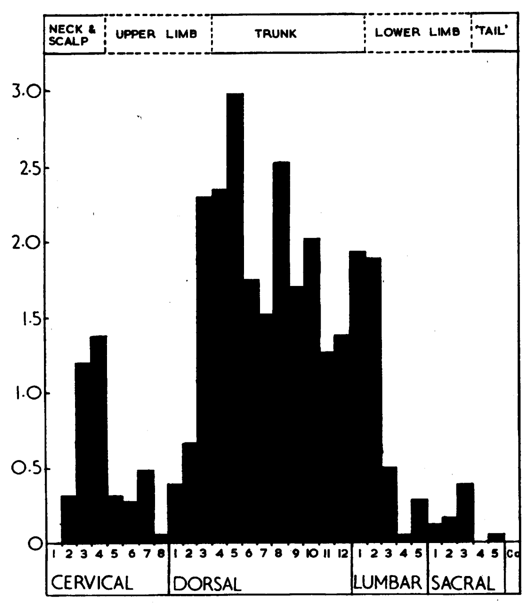

Fig 4 *Specific incidence of zoster on the sensory ganglia of the trunk and limbs*

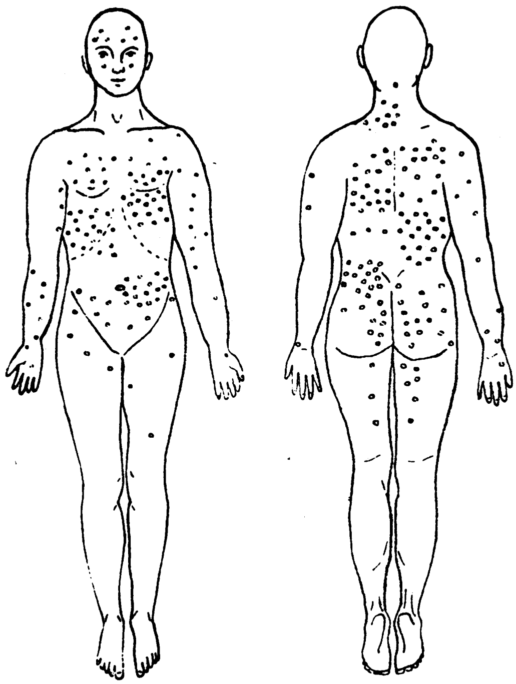

Fig 5 *The segmental distribution of 46 cases of herpes zoster. (Reproduced from Stern, 1937, by kind permission)*

the origin of the lower limb between L.2 and L.3 the rate drops from 1·89 to 0·49. All the errors and inaccuracies combine to minimize such differences, yet they cannot altogether smooth the edge of such abrupt changes.

The real magnitude of the regional differences may be gathered from the average figures for each region. The lower limb, for example, averages 0·16 per ganglion pair, only one-twelfth of the average of 2·0 for the ganglia of the trunk.

Here, in the pattern of the distribution by frequency of attacks of zoster one is suddenly reminded of another pattern of distribution, namely that of the varicella rash – the classical centripetal distribution distinguishing it from the centrifugal distribution of smallpox. The varicella rash is abundant on the trunk and face, sparse on the limbs, rare on the palms and soles, and one cannot assume that chance alone has dictated that the specific ganglionic incidences of zoster shall also follow this pattern. Stern in 1937 accumulated his 46 cases of zoster into the illustration shown in Fig 5, which emphasizes the point very clearly.

Precipitating Influences

The classical precipitants of zoster – lead, arsenic, syphilis, spinal trauma and neoplasm, and more recently leukæmia and X-irradiation – are well-attested and indubitable, and to them may perhaps be added steroid therapy. In the last century and the early years of the present one the importance of precipitants was understood, and indeed at that time the most heated arguments about the nature of zoster occurred between those dualists who believed precipitated zoster to differ from the other sort, and monists who did not. In the present series precipitants appear to have played little or no part. Each case was carefully considered and in only 2 were they suspected, a young man bitten by a horsefly and a girl with an injured leg, both of whom developed zoster within a fortnight in the insulted part. Out of 192 cases, even these 2 may have been coincidental. Extraneous precipitants are apparently relatively uncommon and cannot form the basis of our hypothesis, though they will be considered again in relation to it.

Liability to Further Attacks

An attack of herpes zoster is often considered to give rise to permanent immunity, so that subsequent attacks should be very rare. This is not so. Head & Campbell (1900) record three second attacks among 400 cases of zoster, a rate of less than 1%. In our series of 192 cases, 8 were recorded as second attacks and one as a third attack, which gives a rate of nearly six times that of Head & Campbell. Yet it may well be an underestimate, because enquiry on the point was not specifically made in the earlier years of the study. Even so, the incidence of zoster amongst those who had already had an attack was at least as high as that of first attacks in the general population. This was an unexpected finding. Another unexpected finding was the tendency of subsequent attacks to recur in the segment previously affected. Four of our nine subsequent attacks involved a sensory ganglion which had been the site of previous zoster. The odds against this being a chance finding are very high.

The Picture of Zoster

What is the total picture of zoster that emerges from these studies and that our hypothesis must explain? We find, in persons who have already had varicella, a different malady due to the varicella virus appearing at an average annual rate of 3–5 per thousand of the population, independently of the local prevalence of varicella. Children in contact with zoster are apt to catch varicella, if they have not already had it, but this is a one-way traffic and zoster is not usually caught either from varicella or from other cases of zoster. Although no age is exempt from zoster, the young are attacked seldom and sparingly, and the frequency and severity of the attacks both tend to increase with age.

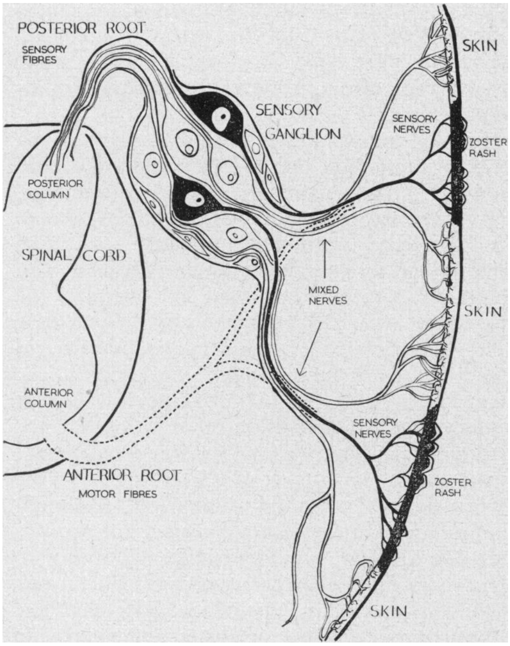

Fig 6 *Diagram of pathology of zoster. Affected neurones and affected sensory nerves in black*

Typical zoster strikes unexpectedly, and seldom can a precipitant be found. The rash is usually limited to an area of skin and mucous membrane served by a single sensory ganglion, of which only a portion, sometimes a minute portion, may be affected (*see* Fig 6). When, rarely, more than one ganglion is simultaneously involved, the affected segments are usually wide apart and may be on opposite sides of the body. Second attacks are as common amongst those already attacked, as first attacks are in the general population. The distribution of the incidence of zoster attacks upon individual ganglia roughly resembles the distribution of the varicella rash.

The Present Hypothesis

Supposition concerning varicella: The varicella virus belongs to the poxvirus group and I suggest that varicella follows the lines discovered for mousepox by Fenner in 1948. If so, the infecting dose of varicella virus gains lodgement, probably in the nasopharynx, where it produces an insignificant lesion and dwells and multiplies for perhaps a week. It then invades the blood stream to produce the primary viræmia, which is a small affair. This first little batch of virus is removed from the blood stream by the cells of the reticulo-endothelial system, within which the virus again multiplies. A second much larger viræmia occurs a week after the first, causing fever and malaise, and scattering the virus to all parts of the body. It lodges especially in skin and mucous membrane, causing pocks, which are the spots of varicella.

At this point it is important to remember the evolutionary aspects of the process just described. The varicella virus is an obligate parasite of man, and this is the host-parasite interaction upon which it depends for its survival as a species. To this end, from all the spots, infectious virus is shed into the environment to infect susceptible persons, and so accomplish the primary host-parasite reproductive cycle of the varicella virus. But this is not all.

Supposition concerning the establishment of latent neural virus: From every spot in the skin and mucosæ of the nasopharynx, conjunctivæ, bladder, &c., virus also enters the contiguous endings of the sensory nerves, whence it is transported up the sensory fibres until it arrives at the sensory ganglia, where it becomes established as a latent infection in the nuclei of the neurones. By now it is in an incomplete pro-virus state, comparable to that of temperate bacteriophage, which harmlessly parasitizes lysogenic bacteria. In nerve and ganglion it is insulated from the now rapidly rising tide of neutralizing antibody in the circulation.

It is true that the virus has already twice had the opportunity for establishing itself by the circulatory route in the ganglia during the primary and secondary viræmia. If, however, the hæmatogenous route is postulated, we would need to explain how, out of all the situations in the body, the ganglia only seem to be affected by zoster, and out of all the ganglionic masses in the body the sensory ganglia, almost alone, are affected. It is precisely these sensory ganglia which offer the first opportunity for a nuclear lodgement on a neural journey from the periphery. When, as sometimes occurs, a mixed ganglion is affected by zoster, the motor portion is usually spared and the sensory portion alone involved. In explaining the precision with which the sensory ganglia are selected, the nerve route demands less special pleading than the hæmatogenous route. A further argument in favour of the neural route may be seen in the pattern of incidence of zoster on the individual sensory ganglia, which reflects the abundance or otherwise of the varicella rash. The relationship may, in fact, be direct. Areas with dense varicella rash may establish more prolific latent virus in the related ganglia, and in return bear more attacks of zoster in later life.

In contrast to the infectious virus, which is intensely irritant and rapidly multiplying, the latent form of the virus is not infectious, is non-irritant and it does not multiply. It remains harmlessly within the neuronal nucleus, and, because neurones do not replicate, neither does the latent virus. It has not, however, lost the capacity to revert to normal infectiousness, just as, given proper conditions, temperate phage may revert to a fully infectious state. The relationship between the latent virus and the cell is potentially explosive.

One should bear in mind this picture, that, soon after the initial attack of varicella, most of the sensory ganglia in the body begin harbouring, for the rest of their lives, a harmless component of varicella pro-virus – fifty or more foci of incomplete virus, all of them liable, now and then, perhaps on the death of the foster-mother neurone, perhaps when surrounded by new neighbour cells, to revert to full infectiousness.

Supposition concerning the reactivation of latent virus: Now and again one latent virus component will revert. Usually nothing perceptible happens. The minute dose of infectious virus which results is immediately neutralized by circulating antibody before it can multiply enough to cause perceptible damage. Even such a tiny encounter of antibody with virus may stimulate the immune mechanisms to produce yet more antibody. If, however, antibody has declined below the critical value necessary to blanket the explosion, at the next reactivation infectious virus will be able to multiply, perhaps at the expense of the nuclei of the satellite cells in the ganglion, setting up the most intense inflammation. The infectious virus is then transported antidromically down the sensory nerve, causing in its passage a fierce neuritis and neuralgia, and is released around the sensory nerve endings into the skin to produce the characteristic clusters of zoster vesicles. Zoster lesions are, in consequence, always in the most precise anatomical relationship with the neurones damaged or destroyed in the sensory ganglion (*see* Fig 6). From the skin infectious virus is for the second time shed into the environment.

Once again it is as well to consider the evolutionary aspects of the situation. We have to do with an age-old obligate human parasite, any regular manifestation of which must be suspected to have adaptive evolutionary significance. What in fact is the parasite up to? In the not so remote biological past, some thousands of years ago, neolithic man was living in little family groups of 30–60 persons upon the watersheds, prevented from frequent intercourse with his neighbours on other watersheds by the forests and bogs of the intervening valleys. In such communities an outbreak of varicella would have used up all available susceptibles in a few weeks, and the causal virus would have disappeared for ever. Bartlett (1957) has shown that an aggregation of some 200,000 people is needed for the continuous support of such a virus, and yet varicella shows all the marks of an ancient parasitism of man; we know of no alternative host, and it does not seem, like measles and variola, to be a recent mutant of an animal epizootic virus.

How can we explain the paradox that the host-parasite interaction that we call varicella could not by itself have secured the survival of the virus, and yet the varicella virus is still with us? There must be some additional mechanism of virus survival, and surely in zoster we have just such an adaptation. During the attack of varicella, the virus is not only shed to start an immediate new cycle, but also goes to ground in a state of latency in each human host. Biologically the latent state is useless to virus survival unless, sooner or later, reactivation takes place, and the virus once again reaches the general environment of the host. The attack of zoster is surely the missing piece of the puzzle. The neolithic human communities, cut off from frequent intercourse with one another, would produce in twenty to thirty years a new generation susceptible to attack by the varicella virus. One of the older members of the group would develop zoster, and so provide infectious virus to start the little outbreak of varicella from which the new generation would receive, in its turn, the latent parasites. Indeed, in just this way varicella virus still secures survival in remote island communities. Zoster must, therefore, be regarded as an integral part of the host-parasite relationship, a secondary or tertiary stage of the varicella virus infection.

Supposition concerning the mechanism of second attacks: During the attack of varicella the neutralizing antibody begins to rise about the seventh day, reaches high values during the third week and then slowly declines. Downie (1959) and others have shown that after an attack of zoster antibody mounts to still higher values. Presumably when the body has again dropped its defences and the antibody has again declined below the critical value, the next time that the latent virus reactivates, it will once again successfully escape down the partially insulated route of the sensory nerve to produce a second attack of zoster.

Supposition concerning zoster generalisatus: One must bear in mind this race between the virus and the antibody. Every time there is 'successful' reactivation, resulting in zoster, some infectious particles will also escape into the blood stream. All of them may be immediately smothered by antibody, but more commonly, as Lewis (1958) has shown, a few escape to cause scattered ectopic vesicles in different parts of the body. Occasionally, a sufficient number escape to produce a severe generalized varicelliform rash. The density of the ectopic rash must always depend upon the balance between the initial content of antibody in the blood and the speed of the deployment of new antibody in response to the multiplying virus. The antagonists may be so nicely balanced that a small tilt in one direction or the other may have a large effect.

Supposition concerning simultaneous multiple attacks: The chance of reactivation occurring simultaneously in more than one ganglion is not high, so multiple zoster is rare. When simultaneous reactivation does occur it is a random process, so that the ganglia affected may well bear no anatomical relationship to one another. Both attacks will be governed by the general pattern of frequency distribution, and this we find to be true. Adjacent segments will be attacked simultaneously only as a rare chance event.

Precipitants considered in relation to the present hypothesis: Of all the classical precipitants of zoster, two, leukæmia and X-rays, are at present the most important. Both of them depress antibody production and accordingly their tendency to produce zoster is explicable in terms of the mechanism proposed in this Lecture. The dangerous effects of steroids on persons suffering from zoster, especially lethal when the zoster is associated with leukæmia, can also be understood along these lines. Leukæmia and neoplasm may also provide an abundance of new cells alongside neurones containing latent virus, and so, by induction (Sabin & Koch 1963), promote reactivation to the infectious state.

Subsidiary Hypotheses

Supposition concerning postponement of zoster by new encounters with the virus: The hypothesis outlined above seems to explain most of the main factors of the natural history of zoster. One characteristic of the disease, however, does not seem to be adequately explained; namely the long interval that usually occurs between the initial attack of varicella and the first attack of zoster. This is quite often fifty years and, indeed, more than half of us die never having had an attack of zoster. Should a cohort of 1,000 people live to be 85 years old, only half of them would have had an attack of zoster, 10 would have had two attacks and one might have had a third attack. Although this is an adequate rate for its evolutionary functions, zoster ought on our hypothesis, to appear more commonly. The age-incidence curve of first attacks should probably be distributed normally and, if so, the mode would occur somewhere about the age of 90, were the curve not curtailed by the brevity of human life. It is difficult to believe that simple persistence of antibody could alone account for so protracted a curve. One must look for factors of a type to interfere with the decline of antibody and so prolong the latent interval. One internal source of postponement may be seen in the fifty or so ganglionic foci of

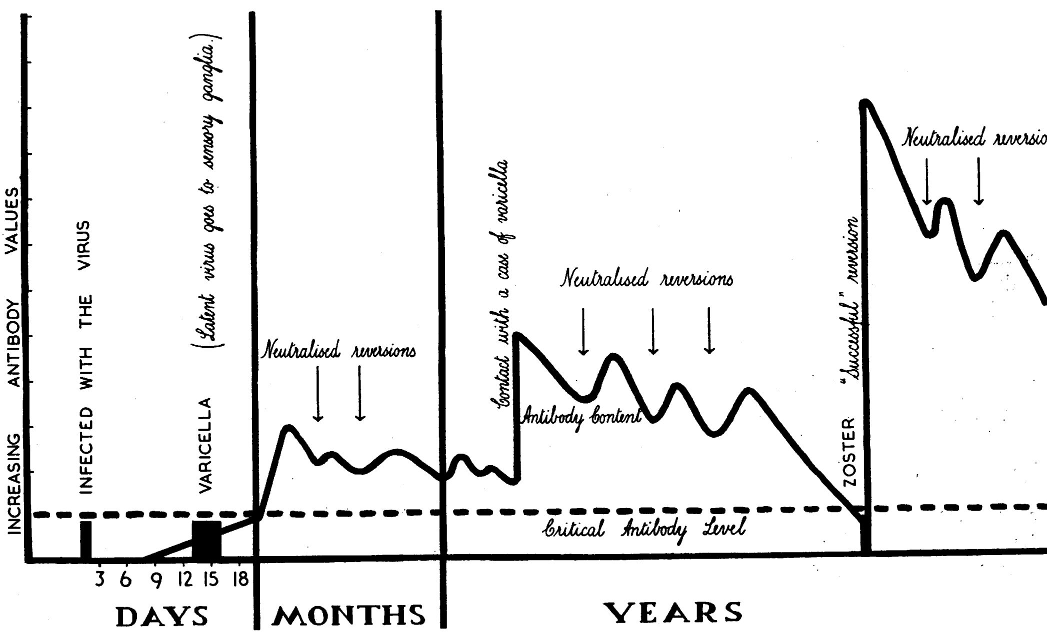

Fig 7 *Diagram of suggested nature of herpes zoster*

latent infection. Each reactivation of virus in these is likely to stimulate antibody production – a negligible effect, perhaps, while antibody values are high, but proportionately greater as the antibody declines towards the critical value, and such secondary stimulation may cause protracted elevation of antibody content (Fig 7).

A second possible source of postponement may be due to extraneous stimulation. Each time that a person who has had varicella again encounters an infectious case of varicella, or maybe zoster, he may again come into effective contact with the virus, and the result may be a 'boost' to his immunity, reversing the decline in his antibody and so postponing the liability to zoster until immunity again wanes. Postponement of zoster from such further encounters with varicella virus would be likely to occur again and again in the lifetime of most persons. Stimulation due to new encounters with the virus from whichever source will be likely, as Higgins (1962) has shown, to provide antibody of a type different from that due to the initial attack of varicella, and the curves of its rise and decline may differ from those of the primary response.

The evolutionary aspect: Once again one must look at the matter from the evolutionary standpoint. A boosting of immunity by new encounters with the virus provides a beautiful refinement of the evolutionary adaptation which we call zoster. At times of abundant varicella, when zoster would not be a necessary condition of the survival of the varicella virus, the virus would itself postpone attacks of zoster in the surrounding populace. When, on the other hand, varicella had long been absent and susceptibles were therefore accumulating, zoster would automatically become more frequent and provide the infectious virus to start a new epidemic of varicella.

The peculiar age distribution of zoster may in part reflect the frequency with which the different age groups encounter cases of varicella and, because of the ensuing boost to their antibody production, have their attacks of zoster postponed.

Conclusion

The main purpose of a hypothesis is to put forward a framework on which to base further thought, observation and experiment. While it ought to explain the facts of the disease, it is of still more value if it can be checked, and supported or overturned by observation, experiment or both. The suppositions offered here are susceptible of further testing at many points. Remote rural and pelagic communities can be examined to see if they provide higher zoster rates than urban populations. The rise and fall of antibody values in those in and out of contact with varicella can be examined. The sensory ganglia of adults coming to autopsy can be searched for virus by tissue culture and fluorescent antibody techniques. We have already begun collecting material for these and similar studies.

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